PHOSPHATE BINDERS



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phosphate

- Phosphorus is the sixth most abundant element in the human body

The adult body contains 1000 g of phosphorus:

- 80-90% is in bone.
- 10-14% is intracellular
- 1% is extracellular.

Phosphate functions in human body

- Nucleic acid synthesis
- Energy metabolism
- Cellular signaling
- Membrane integrity
- Muscle function
- Enzyme activity
- Lipid metabolism
- Bone mineralization
- Buffer in bone, serum, and urine.



Recommended daily requirement of phosphorus

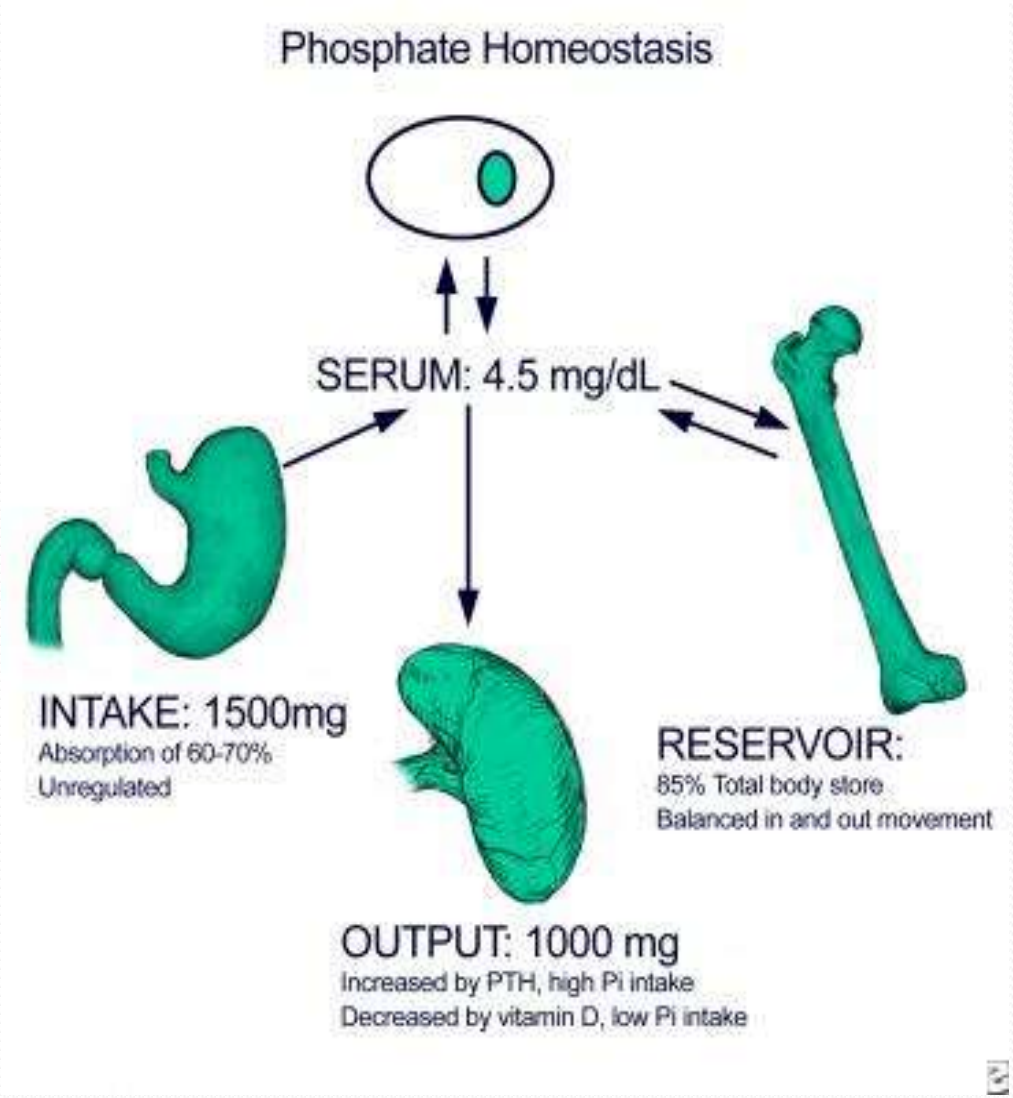
- Adult < 70 y : 700 -4000 mg\day
- Adult > 70 y : 700- 3000 mg\day

Normal level of phosphate

Serum phosphate concentration varies with age, time of day, fasting state, and season.

Serum phosphate concentration

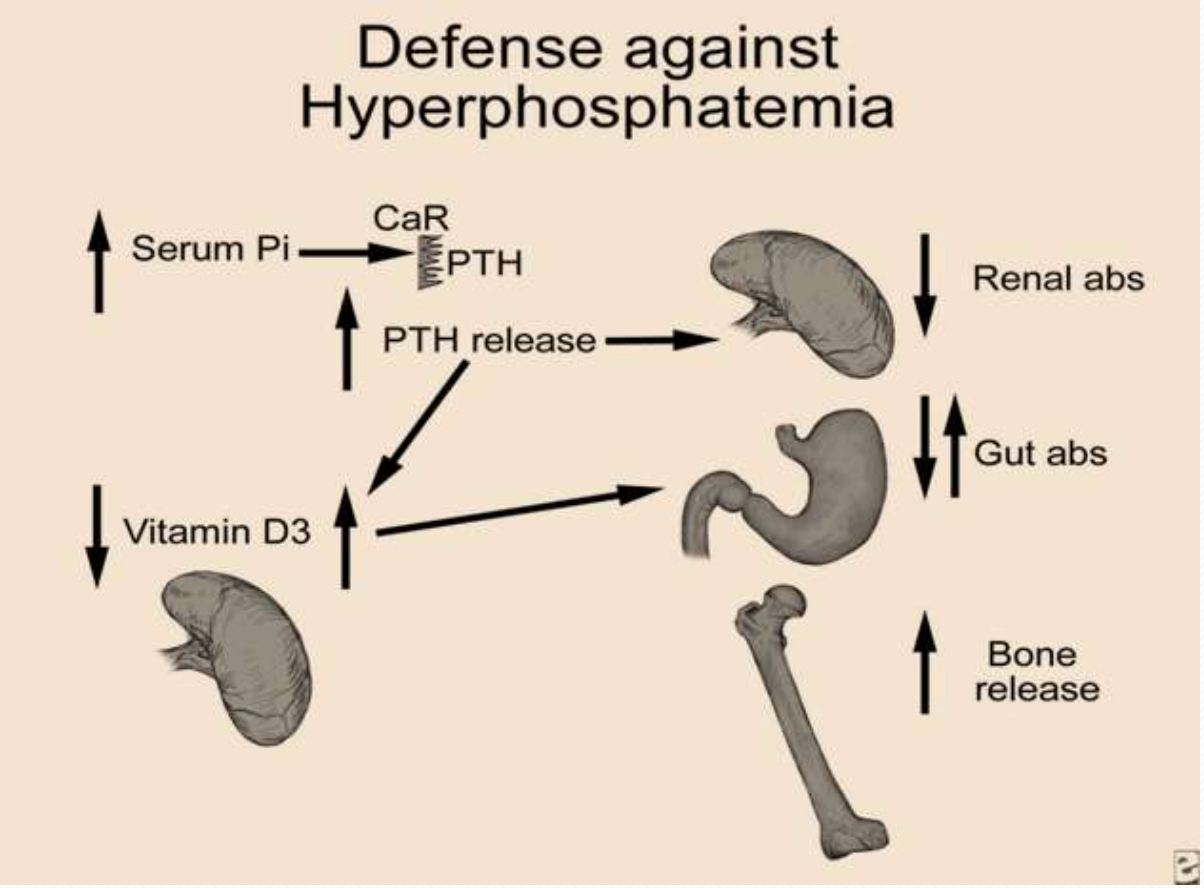
- Children : 4-7 mg/dl
- Adult : 2.5-4.5 mg/dl
- Men have slightly higher pi concentration than women)



- Approximately **60-70% of dietary phosphate, 1000-1500 mg/day, is absorbed** in the small intestine.
- The movement of phosphate in and out of bone, the reservoir containing most of the total body phosphate, is generally balanced.
- Renal excretion of excess dietary phosphate intake ensures maintenance of phosphate homeostasis.

Phosphate homeostasis

- Rapid(short term): phosphatonins
- Long term : PTH , Vit D


Defense against Hyperphosphatemia
Serum Pi
CaR
PTH
PTH release
Renal abs
Gut abs
Vitamin D3
Bone release

Phosphatonins

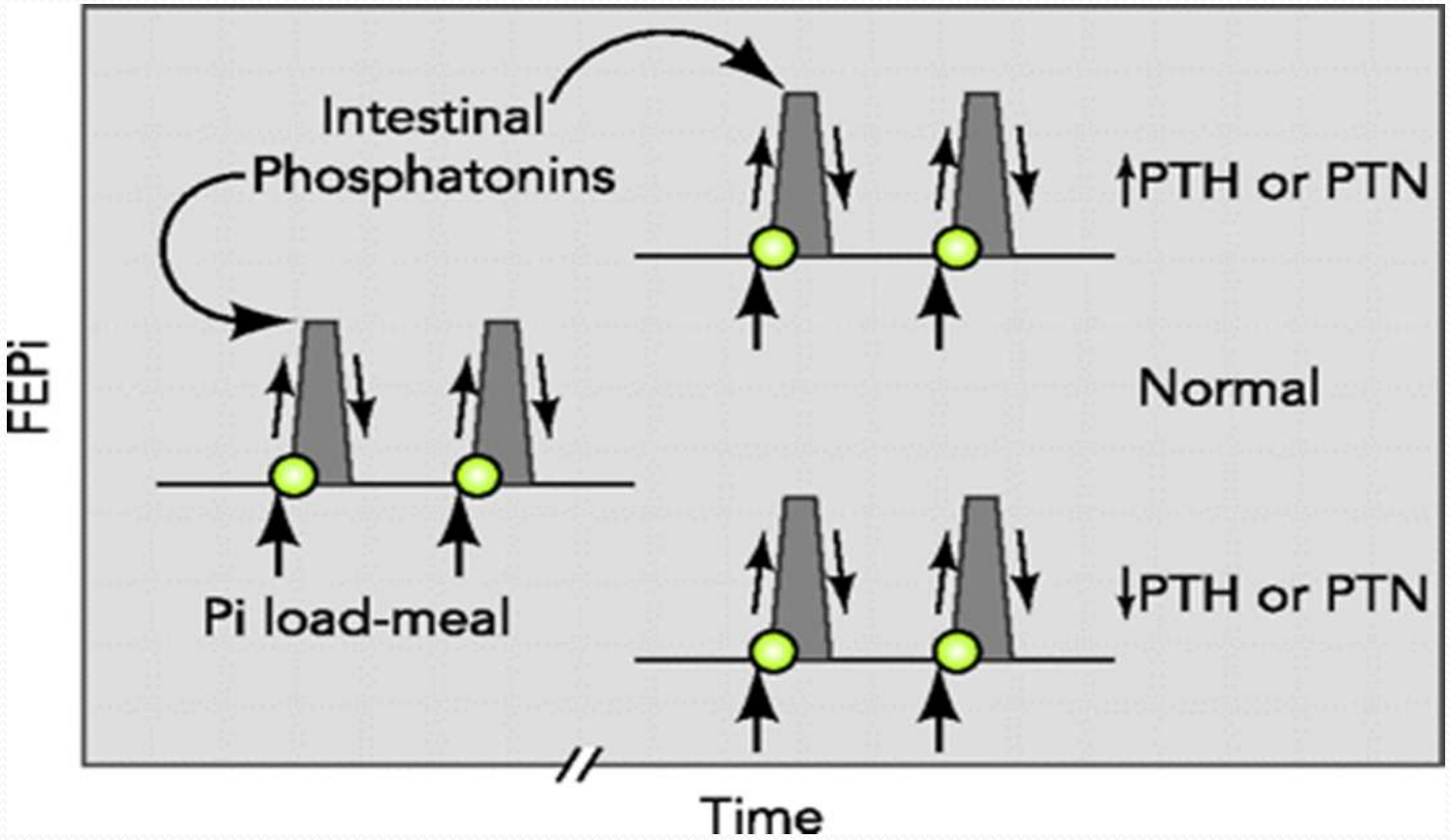
Phosphatonins are new hormones playing an important role in the control of Pi homeostasis together with parathyroid hormone (PTH) and 1,25-dihydroxy vitamin D_3.

phosphatonins

- NaPi-IIc: NaPi cotransport type IIc
- NaPi-IIa: NaPi contransport type IIa
- FGF23: fibroblast growth factor 23
- PHEX: phosphate-regulating gene with homologies to endopeptidase on the X chromosome
- FGFr: FGF receptor
- DMP1: dentin matrix protein 1
- ENPP1: ectonucleotide pyrophosphate/phosphodiesterase 1
- GALNT3: UDP-N-acetyl-alpha-Dgalactosamine:polypeptide N- acetylgalactosminyl transferase 3
- Klotho: FGF23 cofactor

Other phosphatonins

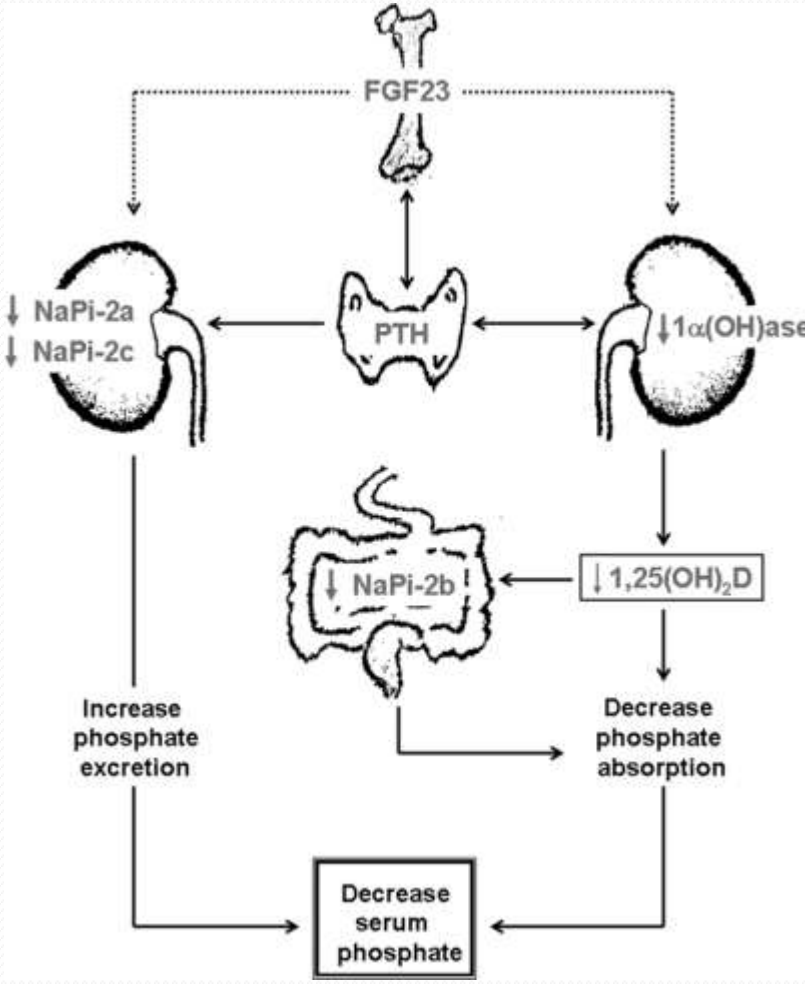
- SECRETED FRIZZLED RELATED PROTEIN 4 (sFRP-4)
- MATRIX EXTRACELLULAR PHOSPHOGLYCOPROTEIN (MEPE)
- FGF-7



Intestinal phosphate sensing increases the fractional excretion of phosphorus in the kidney following increases in intestinal luminal phosphate concentrations by the release of an intestinal mediator (“intestinal phosphatonin

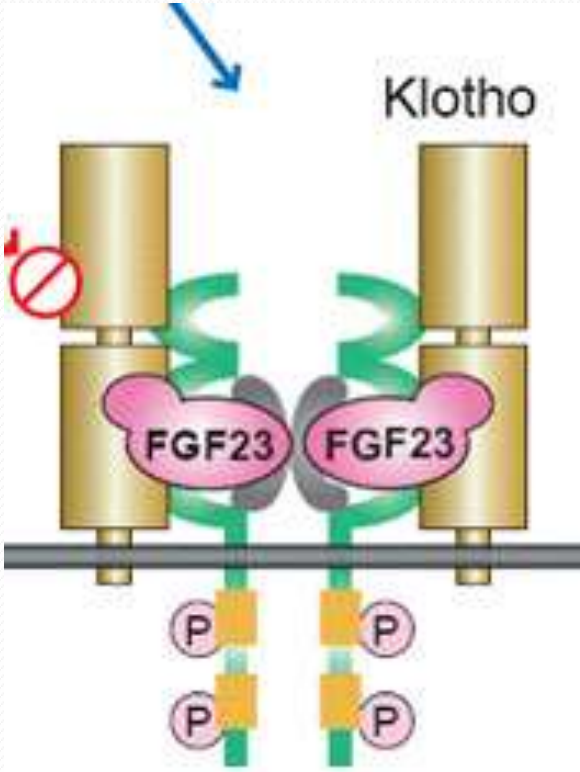
FGF23

- FGF23 secreted from bone(when serum Pi is high)
- It reduces the number of (NaPi) cotransporters, type-2a (NaPi-2a)
- It is action independent of PTH
- It acts on the kidneys to induce phosphaturia
- It suppress active vitamin D synthesis(supress 1-alpha hydroxylase , increases the expression of 24-hydroxylase, leading to inactivation of active D3.



FGF23–Klotho System

- FGF23 requires Klotho as a coreceptor
- Klotho determines the ligand specificity of FGFR1, enabling a tissue-specific response to FGF23
- . Without Klotho, these FGFRs cannot bind to FGF23



Klotho can induce phosphaturia by 2 ways:

- by functioning as a coreceptor for FGF23
- phosphaturic substance independent of FGF23

FGF23–Klotho System and CKD

In patients with CKD,

- circulating levels of FGF23 are progressively increased as kidney function declines.
- Klotho expression in the kidneys is significantly decreased in such patients.

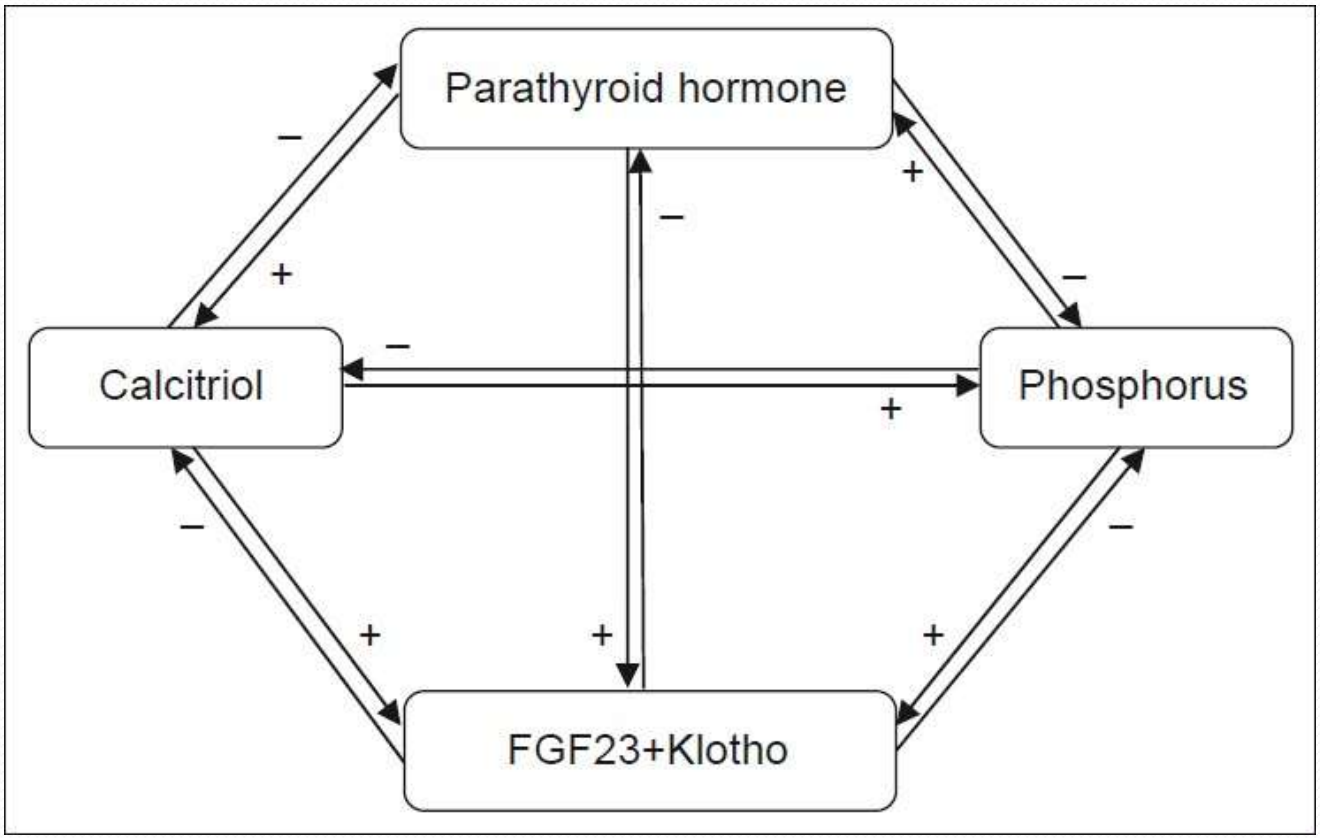
- Therefore, CKD may be viewed as a state of FGF23 resistance caused by Klotho deficiency. Increases in FGF23 precede increases in serum phosphate (hyperphosphatemia) during CKD progression.

Phosphate transporters

The type II family of transporters that include :

- The type IIa and IIc are expressed mostly in the apical membrane of the renal proximal tubule,
- type IIb play a role in transcellular flux of Pi in the small intestine .

the expression of type 2a , type 2c transporters decreased by high dietary phosphate intake, parathyroid hormone (PTH), FGF23, and dopamine..


Parathyroid hormone
Calcitriol
Phosphorus
FGF23+Klotho
–
+
–
+
–
+
–
+
–
+
–
+
–
+
–
+

Under conditions of renal failure, sustained hyperphosphatemia results in sustained hyperparathyroidism. The hyperparathyroidism enhances renal phosphate excretion but also enhances bone resorption, releasing more phosphate into the serum,so retention of Pi occur with RF

Hyperphosphatemia

Causes:

- Increase phosphate intake
- Decrease phosphate excresion
- Shift intracellular phosphate to extracellular space

Major causes of hyperphosphatemia include

- GFR < 30 mL/min
- Hypoparathyroidism
- Pseudohypoparathyroidism
- Excessive oral PO_4 administration
- Overzealous use of enemas containing PO_4
- Shifts of PO_4 into the extracellular space (eg, in diabetic ketoacidosis, rhabdomyolysis, overwhelming systemic infections, and tumor lysis syndrome)

Clinical picture of hyperphosphatemia

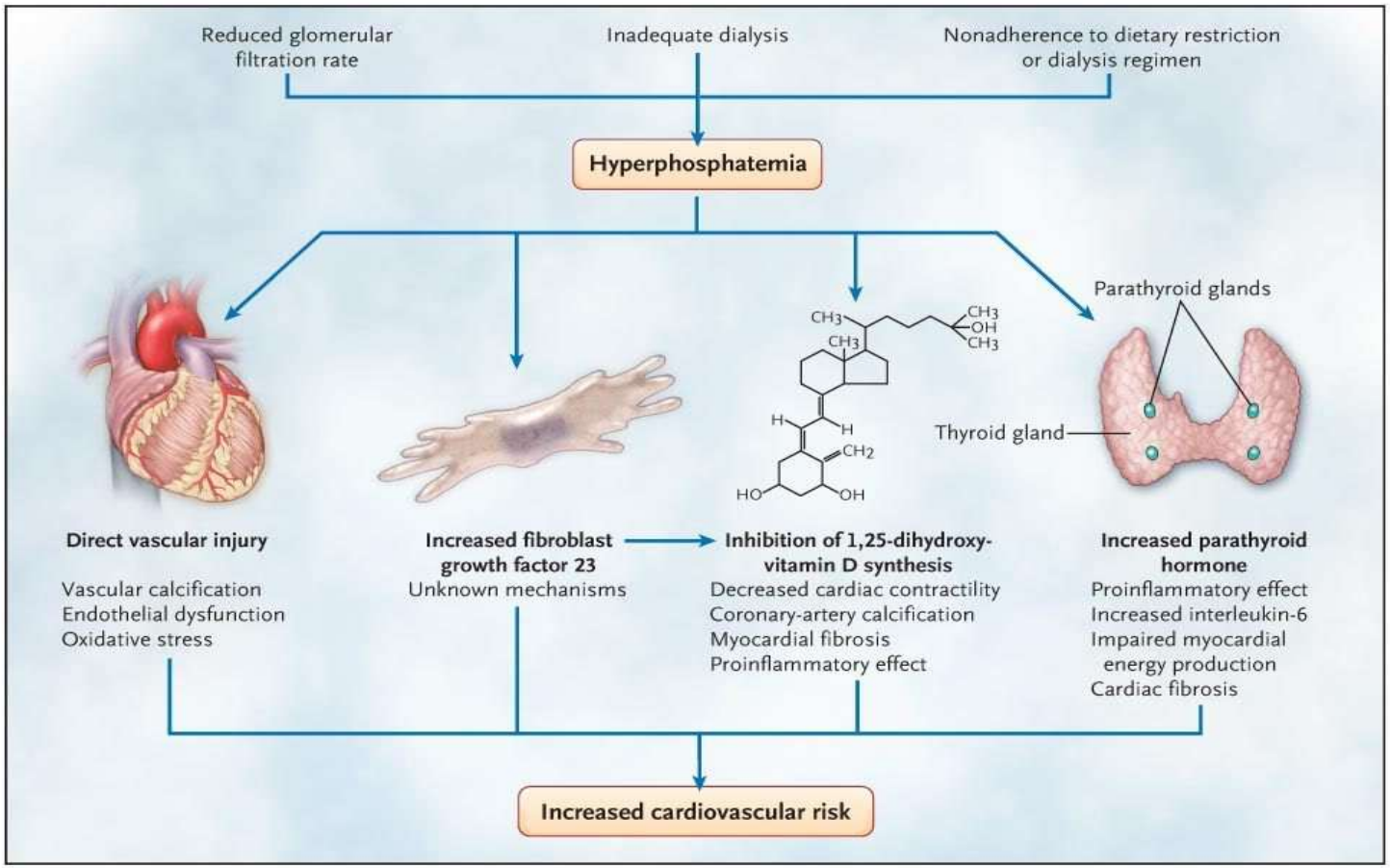
- Asymptomatic,
- Hypocalcemic symptoms: occasionally :,such as muscle cramps, tetany, and perioral numbness or tingling. Other symptoms include bone and joint pain, pruritus, and rash.
- Symptoms related to the underlying cause of the hyperphosphatemia: more commonly these generally are uremic symptoms.

In acute hyperphosphatemia, especially that caused by parenteral phosphate administration, the patient may be hypotensive or exhibit signs of hypocalcemia, such as the following:

- Positive Trousseau
- Chvostek sign
- Hyperreflexia
- Carpopedal spasm
- Seizure



Hyperphosphatemia , cardiovascular calcification



- Hyperphosphatemia promotes vascular calcification in part by promoting SMCs to undergo an osteochondrogenic phenotype change through a mechanism requiring sodium-dependent phosphate cotransporters.
- Upregulation of sodium-dependent phosphate cotransporters in SMCs by disease state and cytokines may facilitate vascular calcification even when serum phosphate levels are in the normal range.

Diagnosis

Results from a full chemistry profile

- Low serum calcium levels
- high phosphate levels
- Blood urea nitrogen (BUN)
- creatinine values
- parathyroid hormone (PTH)
- 25 and 1,25 vitamin D
- 24-hour measurement of urinary phosphate(rarely done)

If renal function is normal, then more unusual disorders, such as :Vitamin D intoxication, Laxative (Phospho-soda) abuse, Tumor lysis ,Rhabdomyolysis,Isolated hypoparathyroidism, Pseudohypoparathyroidism.

False elevation of serum PO_4 also should be excluded by measuring serum protein, lipid, and bilirubin concentration.

DIAGNOSIS; KDIGO guidelines

3.1.1. We recommend monitoring serum levels of calcium, phosphorus, PTH, and alkaline phosphatase activity beginning in CKD stage 3 (1C).

3.1.2. In patients with CKD stages 3–5D, it is reasonable to base the frequency of monitoring serum calcium, phosphorus, and PTH on the presence and magnitude of abnormalities, and the rate of progression of CKD (not graded).

Reasonable monitoring intervals would be:

- in CKD stage 3: for serum calcium and phosphorus, every 6–12 months; and for PTH, based on baseline level and CKD progression.
- In CKD stage 4: for serum calcium and phosphorus, every 3–6 months; and for PTH, every 6–12 months.
- In CKD stage 5, including 5D: for serum calcium and phosphorus, every 1–3 months; and for PTH, every 3–6 months.
- In CKD stages 4–5D: for alkaline phosphatase activity, every 12 months, or more frequently in the presence of elevated PTH (see Chapter 3.2).

Management of hyperphosphatemia

- I.Diet: restricting dietary phosphate intake.
- II.Enhancing elimination: removing phosphate with adequate dialysis.
- III.Minimising phosphate absorption: reducing intestinal absorption using phosphate binders

Diet

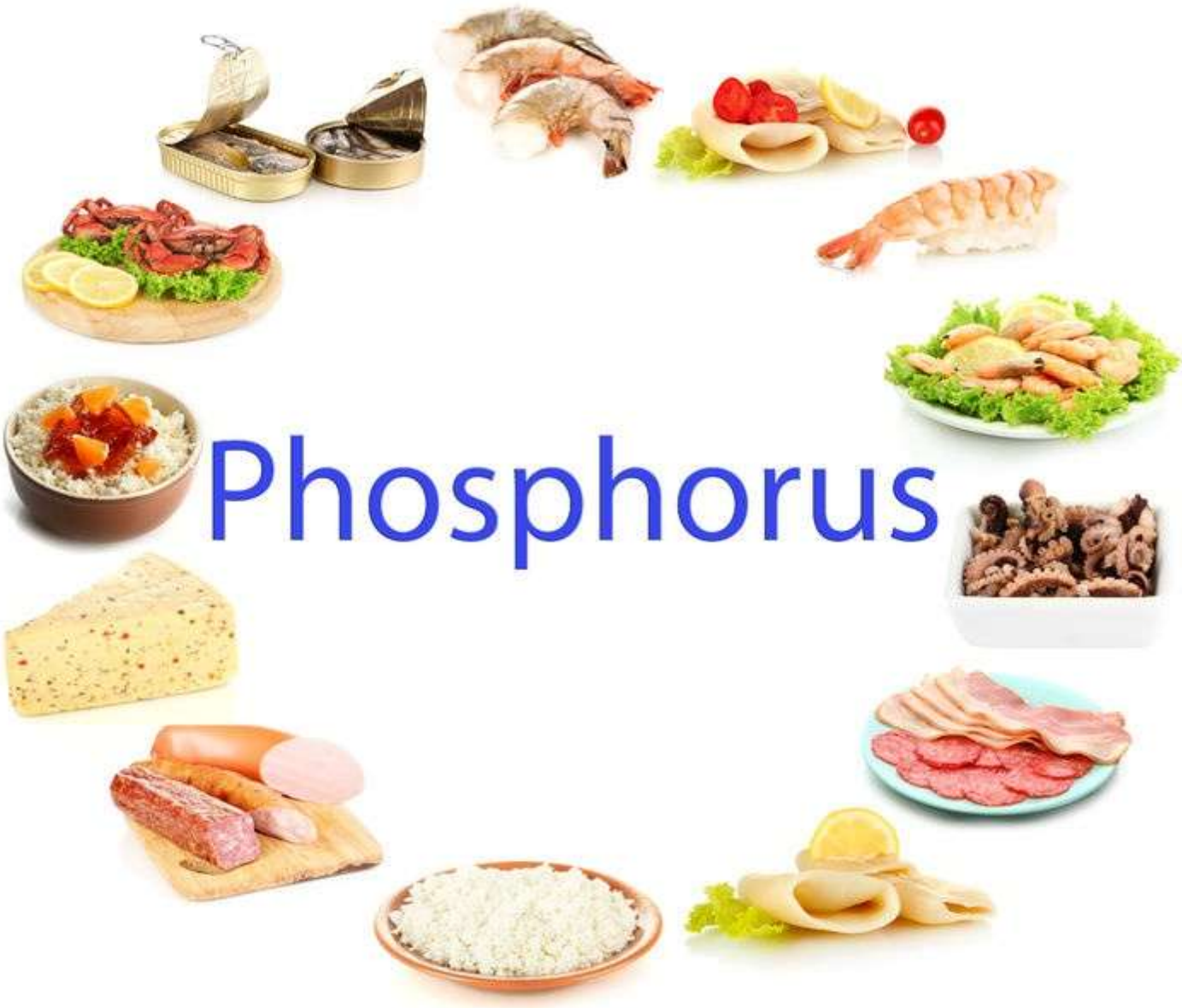
Choose low-phosphorus foods

is to limit foods highest in phosphorus including:

Fast food, convenience foods and processed foods

Beverages

Recommended daily dose of phosphorus : 700 mg\d


Phosphorus

Dialysis

The only dialysis modality shown to normalize serum levels of phosphate is daily, nocturnal home hemodialysis, which is only practical for a small percentage of patients who are physically and psychologically able.

Phosphorus binders



- Hyperphosphatemia is usual in patients with advanced CKD. Standard dialysis plus dietary restriction of phosphate are unable to normalize serum levels in the majority of patients.
- Oral phosphate-binding agents are generally required .

Characteristics of an Ideal Oral Phosphate Binder

- **High affinity for binding phosphorus (low dose required)**
- **Rapid phosphate binding**
- **Low solubility**
- **Low systemic absorption**
- **Non toxic**
- **Palatable, low pill burden**
- **inexpensive**

Types of phosphate binders

- **Calcium-based phosphorus binders:**

calcium acetate , calcium carbonate

- **Aluminum-free, calcium-free phosphorus binders:**

Renagel (sevelamer) and Renvela (sevelamer carbonate), lanthanum carbonate

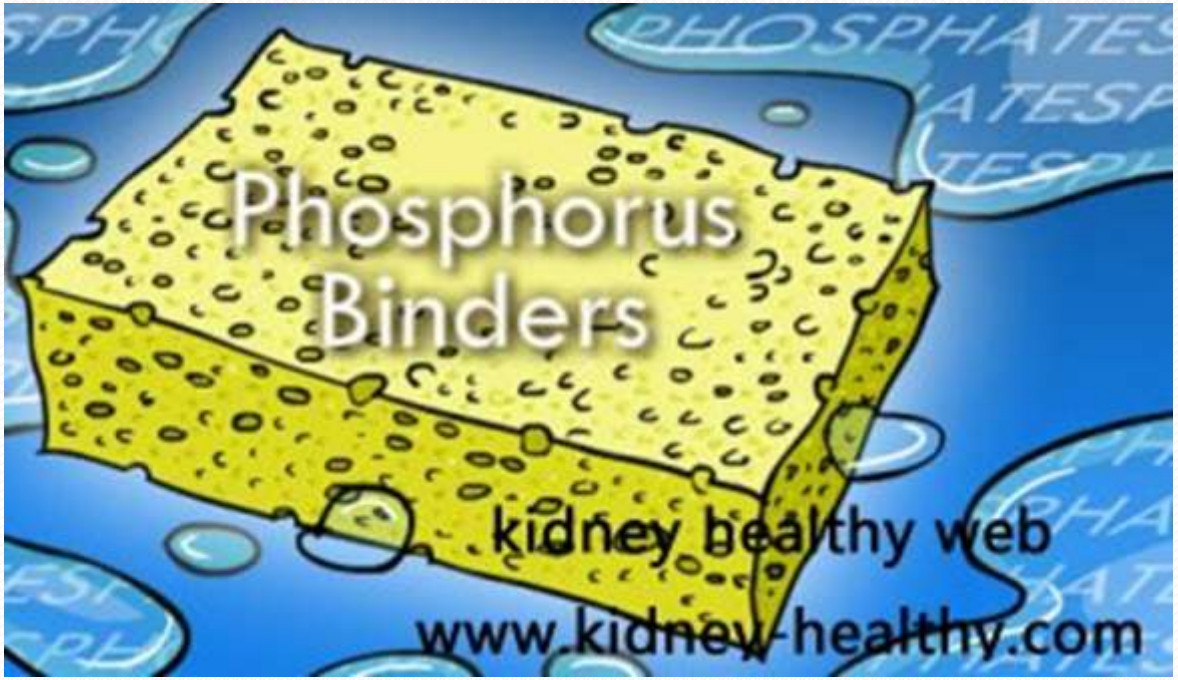
- **Aluminum-based phosphorus binders**
- **Magnesium-based phosphorus binder**
- **Iron based phosphate binders:**

Sucroferric oxyhydroxide, ferric citrate

- Phosphorus binders help to pass excess phosphorus out of the body in the stool.
- They are taken within 5 to 10 minutes before or immediately after meals and snacks.

How do phosphorus binders work?

Phosphorus binders work in one of two ways. Some phosphate binders, such as Renvela, work like a sponge and soak up the phosphates in the food so that eliminated in the stool



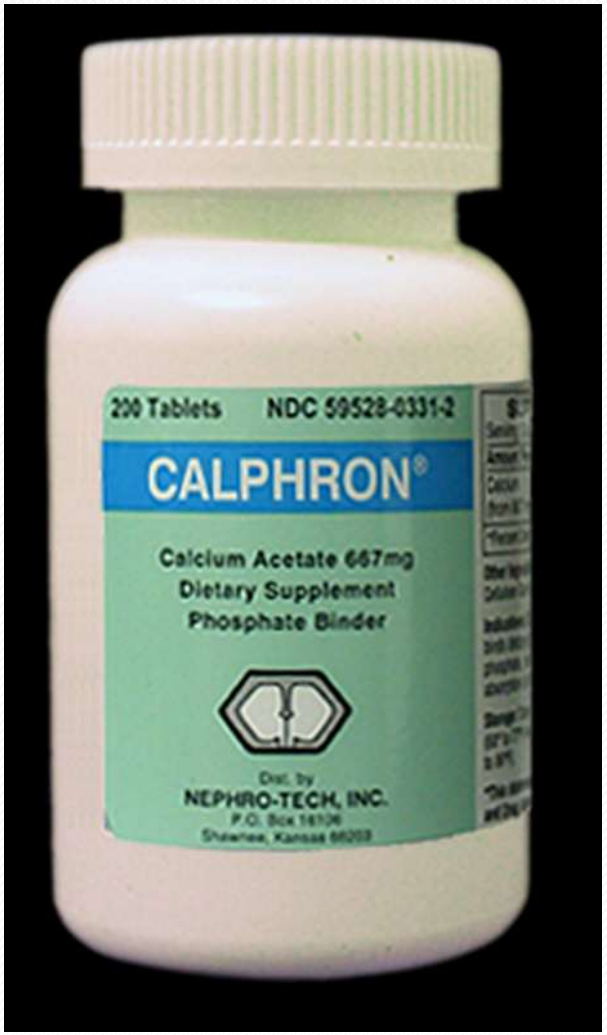
Other phosphorus binders, such as Fosrenol, Phoslo and Tums, work like a magnet. The phosphorus in the food connects to the phosphorus binder and it is carried through the digestive tract to be eliminated.



Calcium-based phosphorus binders

- Calcium acetate: also called PhosLo.
- calcium carbonate.: Tums.

calcium levels must be monitored.



Aluminum-free, calcium-free phosphorus binders:

- Renagel (sevelamer hydrochloride)
- Renvela (sevelamer carbonate)



- Disadvantages:

Sevelamer hcl binds bile acids, is not an efficient phosphate binder in an acidic environment, and contributes to metabolic acidosis.

- Sevelamer carbonate has a 800 mg tablets, but a powdered form of is also available .
- Absence of induction of metabolic acidosis,
- Sevelamer carbonate seems to be equivalent to sevelamer hydrochloride (efficacy and tolerability).



- Chewable fosrenol (lanthanum carbonate) is another aluminum and calcium free binder
- High affinity for phosphate over a wide ph range
- It does not bind bile acids or contribute to metabolic acidosis
- Low pill burden



FOSRENOL®
(lanthanum carbonate)
Chewable Tablets 500 • 750 • 1000 mg
Oral Powder 750 • 1000 mg

- Aluminum-based phosphorus binders

toxic side effects that cause bone disease and damage the nervous system, therefore they are rarely prescribed .Aluminum based binders may be prescribed for short term use .



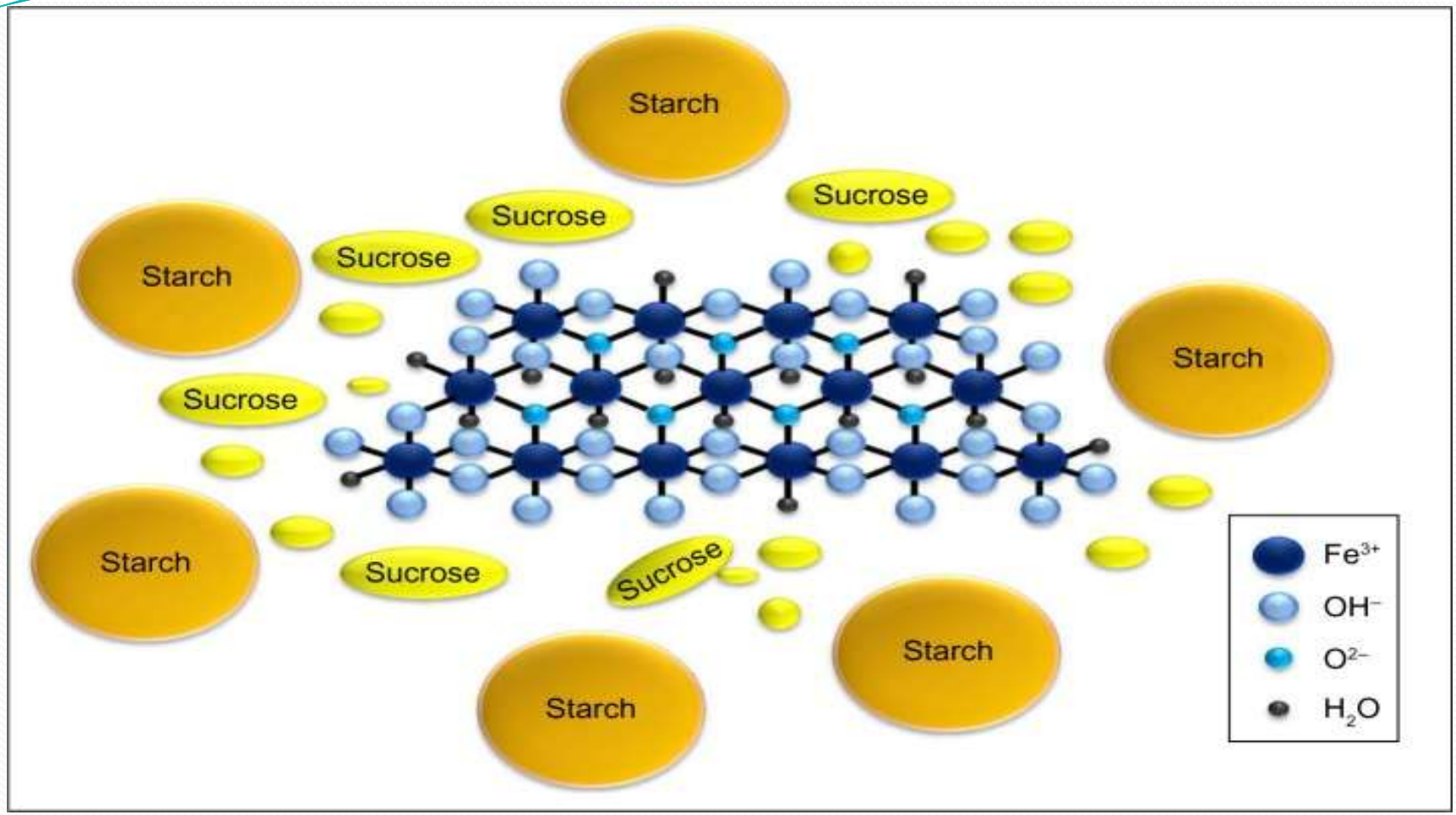
- Magnesium-based phosphorus binders when necessary for a patient to have a lower calcium intake.
- Magnesium levels should be monitored.
- This phosphate binder may be appropriate for peritoneal dialysis (PD) patients, who tend to run lower magnesium levels.



- **iron oxyhydroxide:**

sucroferric oxyhydroxide (Velphoro®, PA21)
This calcium-free iron-based phosphate binder for the treatment of hyperphosphatemia in CKD patients receiving dialysis.





Molecular structure of sucroferric oxyhydroxide consisting of a mixture of polynuclear iron(III)-oxyhydroxide, sucrose, and starches

Note: Iron(III)-oxyhydroxide is the pharmacologically active part.

Mechanism of action:

- The first one is the adsorption of phosphate to the iron complex.
- The second mechanism consists in the formation of iron phosphate through a chemical reaction that is favoured by low pH values

Side effects

- Hypophosphatemia
- Discolored stools
- Diarrhea

Advantage:

- Effective as sevelamer carbonate
- low pill burden
- No change of serum iron level

- It associated with a significant decrease in FGF23 values.
- control of bone metabolism by decreasing FGF23 both directly and by reducing phosphate intestinal absorption.

Table 2. Potential advantages and disadvantages of phosphate binders[4]

Binder Source	Advantages	Disadvantages
Aluminum hydroxide	Very effective phosphate binding capacity Variety of forms	Potential for aluminum toxicity Altered bone mineralization Dementia GI side effects
Calcium-containing (calcium carbonate/acetate/gluconate)	Effective phosphate binding Inexpensive	Potential for hypercalcemia-associated risks including extraskeletal calcification and PTH suppression GI side effects
Lanthanum carbonate	Effective No calcium chewability	Cost Potential for accumulation of lanthanum due to GI absorption; chewability May require calcium supplementation in the presence of symptomatic hypocalcemia GI side effects
Sevelamer (HCl or carbonate)	Effective No calcium/metal Not absorbed Potential for reduced coronary/aortic calcification compared with calcium-based binders	Cost May require calcium supplementation in presence of symptomatic hypocalcemia GI side effects
Sucroferric oxyhydroxide (Velphoro, Vifor Fresenius Medical Care Renal Pharma)	Iron-based, calcium-free Chewable lower pill burden (Average dose is 3.3 pills per day)	Must be chewed Most common adverse drug reactions to Velphoro included discolored feces (12%) and diarrhea (6%).

GI = gastrointestinal; HCl = hydrochloride; PTH = parathyroid hormone

Obstacles to successful management of hyperphosphatemia in chronic kidney disease include :

- Inadequate control of dietary phosphate
- Non-compliance with phosphate-binder therapy.

Phosphate binders in development

1. Iron–magnesium hydroxycarbonate

The iron and magnesium are exchanged for phosphate in the gastrointestinal tract. In a randomized, placebo-controlled study, iron–magnesium hydroxycarbonate showed promising efficacy in the treatment of hyperphosphatemia in patients on hemodialysis

2-the anion exchange resin MCI-196 (2-methylimidazole polymer with 1 chloro-2,3-epoxypropane, also known as colestilan) :

MCI-196 was not associated with hypercalcemia.



3-SBR759 is a polymeric complex composed of iron (III) and starch (on hold)

- **Bixalomer** (kiklin):
- An amine functional polymer. Therapy to CKD patients not on dialysis is (under evaluation.)
- This is a chewing gum formulated with **chitosan**, a natural linear polysaccharide able to bind salivary phosphate in the mouth and gastrointestinal tract.
- It has proven to efficiently contribute to lower phosphatemia in ckd patients.



Alternatives to current phosphate binders

- **nicotinamide** nicotinamide was shown to inhibit sodium-dependent phosphate cotransport activity in small intestine.

- sodium-dependent phosphate transport protein 2B blockers:(The potential to cause pulmonary alveolar microlithiasis).

- **The cationic biopolymer chitosan (RenaGum)** (poly[β-1,4]-2-amino-2-deoxy-D-glucosamine) derives from chitin de-N-acetylation. The hydroxyl and amine polar groups in the structure are electron donors and interact with inorganic salts, including phosphate,each patient was given 20 mg of chewing gum that was loaded with **chitosan** twice daily for 2 weeks

Table 8. Steps To Calculate the Initial Binder Prescription

Step	Example	Example
Phosphorus intake	Total dietary P intake	1,000 per day or 7,000/week
Amount absorbed (50%-70% of mixed diet in nonrenal)(53% renal versus 77% in nonrenal)[169]	Dietary P intake multiplied by average 50%-60% absorbed	600 per day or 4,200/week
Average HD/PD clearance HD = 800 per treatment PD = 300-315 per treatment	Amount abs – dialysis clearance = remaining P to be bound by phosphate binder	HD: 4,200 – 2,400 = 1,800 mg P/wk or 257 mg/d PD: 4,200 – 2,205 = 1,995 mg P/wk or 285 mg/d
Divided by the estimated binding power of the binder of choice:	Remaining P/binding power	257/39 (approx. P bound by 1 g $CaCO_3$) = 6.5 g $CaCO_3$)[170] 257/45 (approx. P bound by 1 g calcium acetate) = 5.7 gm[171] 257/15-30 (approx. P bound by one $Al(OH)_3$ tablet) = 12-17 tabs[172] 257/64 (approx. binding power of 800 mg sevelamer HCl) = 4 caplets 257/32 (approx. binding power per 400 mg sevelamer HCl) = 8 caplets

Note: Binder doses are usually established by trial and error. The above table estimates the initial binder prescription based on average phosphorus absorption, average dialysis clearance, and the approximate binding potential for the binder of choice. Binding potential can be altered by variations in pH. The dose should be monitored and adjusted based on the response of the individual patient.

- In the publication of the KDIGO clinical practice guidelines, which point out that not enough evidence exists to indicate that any specific phosphate binder has a notable effect on patient-level outcomes.
- Thus, which phosphate binder is administered should depend on :

✓ Individual patient,

✓ The effects of available agents on clinical parameters .

❖ Rather than just on whether levels of phosphate are reduced.

What do the other guidelines say? Kidney Disease Outcomes Quality Initiative: In CKD Patients (Stages 3–5): The serum calcium-phosphorus product should be maintained at < 55 mg2 /dL2. This is best achieved by controlling serum levels of phosphorus within the target range. .

Table 1. Serum phosphorus guidelines from KDIGO[4]	
Stage of CKD	**Phosphorus level**
Stage 3 and 4	2.7–4.6 mg/dL (0.87–1.48 mmol/L)
Stage 5, not on dialysis	3.5–5.5 mg/dL (1.13–1.77 mmol/L)
Stage 5, on dialysis	"Toward normal"

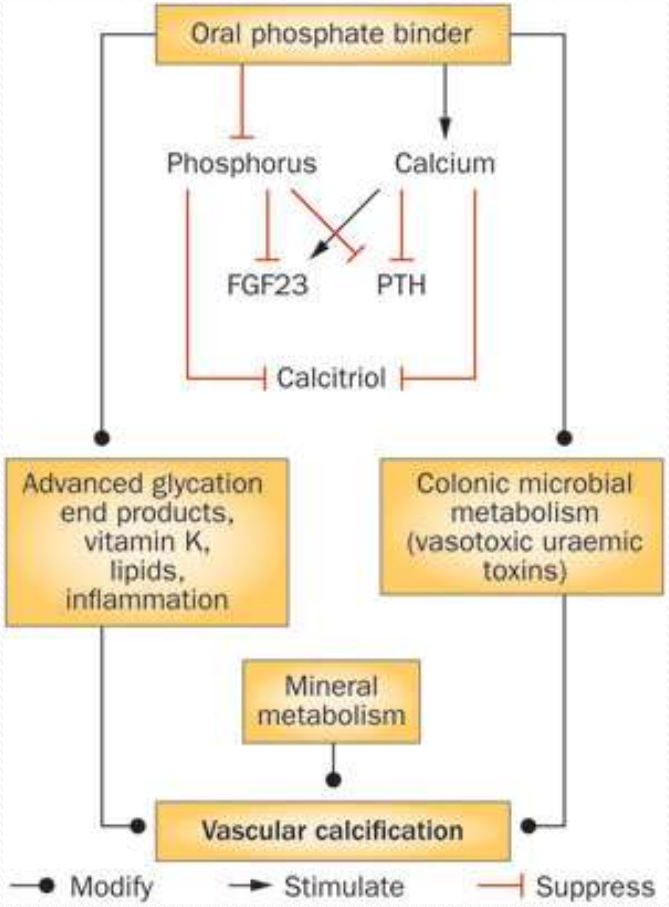
Chronic kidney disease: Phosphate binder therapy—cracks in the tower of strength?

- Oral phosphate binder therapy is considered a 'tower of strength' in the ever-expanding armamentarium of drugs used to treat abnormal mineral metabolism in patients with chronic kidney disease (CKD)
- Recent data from a randomized controlled study by Block *et al*. challenge this strategy, raise doubts about its safety and indicate the need for additional studies of hard end points.

Firstly, active phosphate binder therapy attenuated progressive secondary hyperparathyroidism but failed to affect serum FGF23 concentrations.

- A second that phosphate binder therapy promoted the progression of calcification of the coronary arteries and the abdominal aorta.
- The progression of vascular calcification was evident not only in patients who were receiving calcium acetate, but also in patients randomized to lanthanum carbonate and those on sevelamer carbonate

Figure Hypothetical mechanisms by which phosphate binders might affect vascular calcification



Evenepoel, P. & Meijers, B. (2012) Phosphate binder therapy—cracks in the tower of strength?
Nat. Rev. Nephrol. doi:10.1038/nrneph.2012.219

Conclusion

- All currently available oral phosphate binders are known to be effective, and will reduce serum levels of phosphate to a similar degree.
- Calcium-based binders are inexpensive in comparison with lanthanum and sevelamer, but the long-term effects of calcium overload and its association with vascular calcification.

- New phosphate binders continue to be developed but none seems to represent a large step forward in terms of phosphate control.
- Alternative strategies for the future include gastrointestinal phosphate blockade, and binding of salivary phosphate—both of which could be used as adjunctive therapies in patients requiring additional reduction in phosphate levels.

- No clinical studies have yet defined the ideal level to which serum phosphate should be reduced in patients with CKD who are on dialysis. Neither is it known whether any degree of phosphate reduction improves patient outcomes.
- Clearly, it is important that the role of phosphate control in determining patient outcomes requires a large randomized, controlled study .
- Without such a study we can only continue to rely on observational data with all its uncertainties and potential to mislead

Thank you